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ORIGINAL ARTICLE

NF-1Score: A Prediction Score for Internal Neurofibromas in Neurofibromatosis-1

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NF-1 is associated with a 15-year decrease in life expectancy. Internal neurofibromas are associated with increased morbidity and mortality through malignant transformation and compression of neighboring organs. Our purpose was to develop and to validate a clinical score for predicting internal neurofibromas in adults. The development sample comprised 208 patients and the validation sample 191 patients. The score was developed using logistic regression. Discrimination and calibration of the model were evaluated. Four variables were independently associated with internal neurofibromas: at least two subcutaneous neurofibromas (odds ratio (OR) = 4.7, [2.1–10.5]), age ⩽30 years (OR = 3.1, [1.4–6.8]), absence of cutaneous neurofibromas (OR = 2.6, [0.9–7.5]), and fewer than six café-au-lait spots (OR = 2.0 [0.9–4.6]). The score computed by linear combination of the rounded coefficients of these four variables ranged from 0 to 40 (mean, 12.8 ± 10.8). The probability of internal neurofibromas was computed as exp (−2.93 + 0.11Score)/exp (1 + (−2.93 + 0.11Score)). Probabilities agreed well with the observed frequencies indicating good calibration, and discrimination was adequate (AUC-ROC, 0.75) in both data sets. The presence of internal neurofibromas can be accurately predicted using a simple clinical score. Further work will establish the score threshold that identifies patients at high risk for complications.

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INTRODUCTION

Neurofibromatosis-1 (NF-1 [MIM 162,200]) is a common autosomal dominant disorder that is associated with both morbidity and mortality (Rasmussen *et al.*, 2001). Internal neurofibromas are among the main causes of adverse outcomes (Tucker *et al.*, 2005). These tumors may cause spinal cord compression, and about 10% of them undergo transformation to malignant peripheral nerve-sheath tumors (MPNSTs), which are among the main causes of death in adults with NF-1 (Rasmussen *et al.*, 2001). Internal neurofibromas arise from the spinal nerve roots and may extend into surrounding structures to involve multiple fascicles and branches. They are generally asymptomatic (Tonsgard *et al.*, 1998), being identified only upon imaging studies. Accurate data can be obtained using magnetic resonance imaging (MRI), which shows large diffuse paraspinal tumors with high signal intensity on T2-weighted and T2 fat-saturation images contrasting with normal or, more often, low signal intensity on T1-weighted images (Drouet *et al.*, 2004; Mautner *et al.*, 2006). Clinical indicators of malignancy are persistent or increasing pain, enlargement of the tumor, and neurological deficiencies (Valeyrie-Allanore *et al.*, 2005). MPNSTs carry a poor prognosis. Diagnosis is often delayed, as imaging studies are not performed routinely as part of the follow-up of patients with NF-1. Consequently, metastatic spread is common and survival is limited. The main prognostic factor may be tumor size, which governs the chances of curative surgery (Doorn *et al.*, 1995). Therefore, an early diagnosis is a principal objective. As MPNSTs develop from internal neurofibromas, a score predicting the presence of internal neurofibromas might improve the early diagnosis of MPNSTs, as close monitoring could be offered to patients with high-risk score values.

The purpose of this study was to develop a clinical score for predicting the presence of internal neurofibromas in patients with NF-1 and to assess its performance by evaluating discrimination and calibration.

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Abbreviations: AUC-ROC, area under the receiver-operating characteristic curve; CI, confidence interval; MPNSTs, malignant peripheral nerve-sheath tumors; MRI, magnetic resonance imaging; NF-1, neurofibromatosis type-1; OR, odds ratio; ROC, receiver-operating characteristic

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RESULTS

Study populations

The characteristics of the development and validation samples are reported in Table 1. The development sample comprised 208 patients, 122 females (59%), and 86 males with a mean age of 41.10 (±13) years (range, 20–78). Internal neurofibromas were present in 46 (22%) patients. The validation sample was composed of 191 patients, 108 females (57%), and 83 males with a mean age of 40.3 (±13) years (range 17–72), of whom 39 (20%) were classified as having internal neurofibromas. There were 304 patients whose internal neurofibroma status was unknown and who therefore were not included in the validation sample; their characteristics were not significantly different from those of the validation sample (data not shown).

Model development

In the univariate analyses, five variables were associated, or nearly associated, with internal neurofibromas: age ⩽30 years, at least two subcutaneous neurofibromas, fewer than six café-au-lait spots, absence of cutaneous neurofibromas, and absence of freckles (Table 2). No significant interaction was observed between these parameters. Absence of freckles was strongly associated with the other variables and was not independently associated with internal neurofibromas in the multivariate analysis. The four remaining variables were independently associated with internal neurofibromas (Table 3). Calibration was excellent (Hosmer–Lemeshow statistic = 2.4; df = 4; $P = 0.66$) and discrimination was good (area under the receiver–operating characteristic curve (AUC-ROC) = 0.75; 95% confidence interval (CI), 0.7–0.8). The β-coefficients derived from the four independent predictors were multiplied by 10 and rounded to the nearest integer (Table 3). Loss-of-fit related to the rounded coefficients was negligible (Hosmer–Lemeshow statistic = 4.5; df = 7; $P > 0.5$). Discrimination was similar (AUC-ROC = 0.75; 95% CI, 0.68–0.82). Table 4 shows the sensitivity and the specificity of the different cut-off levels of the score in the development sample. False-positive and false-negative rates can be deducted from sensitivity and specificity (1 – specificity and 1 – sensitivity, respectively). The score was then computed by means of a linear combination of the rounded coefficients: Score = 10 · (age ⩽30 years) + 10 · (absence of cutaneous neurofibroma) + 15 · (⩾2 subcutaneous neurofibromas) + 5 · (<6 café-au-lait spots). Each factor was assigned the value 1 if present or 0 if absent. Therefore, the score could range from 0 to 40. The mean score was 12.8 (±10.8). An equation based on the logistic regression model was developed to convert the score into a probability of having internal neurofibromas in the following manner: exp (−2.93 + 0.11*Score)/exp (1 + (−2.93 + 0.11*Score)).

Table 1. Characteristics of the patients with NF-1 included in the development (*n*=208) and validation (*n*=191) samples

Clinical feature	Development sample *n*=208	Validation sample *n*=191
Female gender	122 (59)	108 (57)
Age ⩽30 years	48 (23)	46 (24)
Familial case	112 (54)	127 (67)
⩾2 Subcutaneous neurofibromas	106 (51)	111 (61)
No cutaneous neurofibromas	19 (9)	30 (16)
Plexiform neurofibromas	114 (55)	95 (50)
<6 Café-au-lait spots	43 (21)	58 (30)
No freckles	39 (19)	31 (16)
Scoliosis	87 (42)	90 (47)
Pseudarthrosis	6 (3)	6 (3)
Headache	79 (38)	77 (40)
Epilepsy	4 (2)	8 (4)
Hydrocephalus	3 (1)	7 (4)
Learning disabilities	109 (52)	98 (51)
Facial asymmetry	20 (10)	13 (7)
Hypertension	17 (8)	23 (12)
Internal neurofibroma	46 (22)	39 (20)

Abbreviation: NF-1, neurofibromatosis-1.
The data are the numbers of patients (%).

Model assessments

Internal validation. The shrinkage coefficients obtained by bootstrapping methods were similar to those based on the logistic regression model: $\alpha' = \alpha^* 1.05$ and $\beta' = \beta^* 0.98$.

External validation. The score maintained adequate discrimination and calibration (Hosmer–Lemeshow statistic = 12.7; df = 9; $P = 0.2$; AUC-ROC = 0.73) when it was applied to each member of the validation sample. Table 5 shows the predicted risk of internal neurofibromas for each possible score.

DISCUSSION

Our study shows that easily recognizable clinical features can be used to predict the risk of internal neurofibromas among adults with NF-1. Four factors were independently associated with internal neurofibromas: at least two subcutaneous neurofibromas, absence of cutaneous neurofibromas, fewer than 6 café-au-lait spots, and age ⩽30 years. The NF-1Score was computed as follows: 10 (age ⩽30 years) + 10 (absence of cutaneous neurofibromas) + 15 (⩾2 subcutaneous neurofibromas) + 5 (<6 café-au-lait spots). This score had excellent calibration and good discrimination.

Special attention was given to selecting the development sample. Our goal was to select a population of NF-1 patients systematically investigated with MRI, as this method is highly reliable for detecting internal neurofibromas. As part of the case–control study that included the patients in the development sample, the MRI data were reviewed by senior radiologists who were masked to the clinical features, to minimize assessment bias. Furthermore, the prevalence of the various clinical features in the development sample was

Table 2. Univariate analysis in the development sample (*n*=208) of factors suspected to be associated with internal NFs

	Internal neurofibroma			
	No (*n*=162)	Yes (*n*=46)	Odds ratio (95% CI)[1]	*P*-value[2]
Female gender	97 (60)	25 (58)	1.3 (0.6–2.4)	0.502
Age ⩽30 years	30 (18)	18 (39)	**2.8 (1.4–5.9)**	**0.004**[3]
Familial cases	88 (54)	24 (52)	0.9 (0.5–1.8)	0.800
⩾2 Subcutaneous neurofibromas	70 (43)	36 (78)	**4.7 (2.1–10.6)**	**$<10^{-4}$**[3]
No cutaneous NF	9 (6)	10 (22)	**4.7 (1.7–12.8)**	**0.001**[3]
Plexiform NF	90 (56)	24 (52)	0.9 (0.5–1.7)	0.684
<6 Café-au-lait spots	28 (17)	15 (33)	**2.3 (1.1–4.9)**	**0.024**[3]
No freckles	26 (16)	13 (28)	**2.1 (0.9–4.5)**	**0.061**[3]
Scoliosis	68 (42)	19 (41)	1.0 (0.5–1.9)	0.935
Pseudarthroseis	4 (2)	2 (4)	1.8 (0.3–10.2)	0.502
Headache	59 (36)	20 (43)	1.3 (0.7–2.6)	0.385
Epilepsy	2 (1)	2 (4)	3.6 (0.5–26.9)	0.175
Hydrocephalus	3 (2)	0	0	0.353
Learning disabilities	83 (51)	26 (57)	1.2 (0.6–2.4)	0.527
Facial asymmetry (*n*=122/78)	12 (10)	5 (6)	0.6 (0.21–1.87)	0.397
Hypertension	13 (8)	4 (9)	1.1 (0.3–3.5)	0.883

Abbreviations: CI, confidence interval; NF, neurofibromatosis.
[1]Odds ratios with their 95% CIs were estimated using logistic regression.
[2]*P*-value by χ^2-test or Fisher's exact test, as appropriate.
[3]Variables yielding *P*-values less than 0.15 were entered into a multiple logistic regression model.
The data represent the numbers of patients (%).

Table 3. Factors independently associated with internal NFs in the multivariate analysis in the development sample (*n*=208)

	Odds ratio	95% CI[1]	*P*-value	β-Coefficient[2]	Points
Age ⩽30 years old	**3.1**	1.4–6.8	0.006	1.12	**10**
No cutaneous neurofibromas	**2.6**	0.9–7.5	0.08	0.95	**10**
⩾2 Subcutaneous neurofibromas	**4.7**	2.1–10.5	$<10^{-4}$	1.55	**15**
<6 Café-au-lait spots	**2.0**	0.9–4.6	0.08	0.71	**5**

Abbreviations: CI, confidence interval; NF, neurofibromatosis.
[1]Confidence interval.
[2]β-Coefficients of the factors independently associated with internal neurofibromas.

consistent with those previously reported in NF-1 patients (Friedman and Birch, 1997), indicating that the development sample was representative of NF-1 patients. A cohort study design is generally used to assess predictors to minimize information bias (Coste *et al.*, 1996). However, NF-1 is a rare disease and routine MRI screening is not recommended in everyday clinical practice (Pinson *et al.*, 2001). By taking the development sample from a case–control study in which all patients underwent MRI, we improved the reliability of internal neurofibroma diagnosis as compared with a cohort study.

The validation sample was composed of patients included in the Réseau NF-France database. Selection bias seems unlikely, as the prevalences of NF-1 features were consistent with those reported previously in other populations of NF-1 patients (Friedman and Birch, 1997). Furthermore, the features in non-included patients whose internal neurofibroma status was unknown were similar to those in the validation sample. However, absence of routine MRI or computed tomography in the validation sample may constitute a limitation of our study. MRI or computed tomography was performed only when routine imaging studies (chest radiograph and abdominal sonogram) or clinical symptoms suggested the presence of internal neurofibromas. This may have resulted in verification bias. Furthermore, we had no data on the size or location of internal neurofibromas in the validation sample.

To validate the NF-1Score, we used a rigorous procedure involving both internal validation (shrinkage) and external validation. Shrinkage of the regression coefficients (α and β) to correct for over-optimism in the model may help to make

Table 4. Sensitivity and specificity values of the different cut-off levels of the NF-1Score obtained in the development sample

	Development sample (*n*=208) AUC-ROC=0.75	
Cut-point	Sensitivity (%)	Specificity (%)
⩾0	100	0
⩾5	91	37
⩾10	87	43
⩾15	80	53
⩾20	50	83
⩾25	41	91
⩾30	26	98
⩾35	11	99
⩾40	2	100

Abbreviations: AUC-ROC, area under the receiver-operating characteristic curve; NF-1, neurofibromatosis-1.

Table 5. Probabilities of the presence of internal NFs according to the NF-1Score level in the validation sample (191 patients)

Probability of having internal neurofibromas		Internal neurofibromas (*n*=39)		No internal neurofibromas (*n*=152)	
	NF-1Score	Observed	Expected	Observed	Expected
0.051	0	3	2.0	36	37.0
0.083	5	2	1.1	11	11.9
0.133	10	3	1.7	10	11.3
0.207	15	6	11.6	50	44.4
0.308	20	8	8.0	18	18.0
0.430	25	7	9.5	15	12.5
0.561	30	3	5.1	6	4.0
0.684	35	2	4.1	4	1.9
0.787	40	5	5.5	2	1.5

Abbreviation: NF-1, neurofibromatosis-1.

models more transferable (Steyerberg *et al.*, 2004). The results of our internal and external validations in an independent sample indicated satisfactory performance, with good calibration and discrimination. Therefore, from a methodological point of view, this score could be considered as a good prediction tool. Although such probability models cannot be used reliably to predict outcome in individual patients, the information provided by such models using easily recognizable clinical features could be useful for clinical decision-making. For instance, a probability of 0.56 (NF-1Score = 30) means that approximately 56 out of 100 patients with this score would be expected to have internal neurofibromas. One cannot say whether any specific individual patient will be one of the 56 patients who may have internal neurofibromas or one of the 44 such patients who may have not. Clinicians often have to discuss whether or not an imaging would be useful. That is, which NF-1 patients need MRI to detect asymptomatic MPNTs. Thus, although MRI is not systematically recommended, faced with a patient with a high NF-1Score value, physicians would be alerted and mandate a radiological follow-up. Whether systematic radiological investigations are required to evaluate the potential risk of MPNTs in this new population at risk remains to be investigated. Furthermore, introduction of new treatment is usually preceded by the demonstration of its effectiveness in a controlled trial. An important aspect of the conduct of such trials is the ability to define and control the severity-of-illness of the patients studied.

In choosing the appropriate "cut-off" score that defines high risk, there is a trade-off between a score that confers high sensitivity or high specificity. A high cut-off score that gave high specify would lose sensitivity, thereby missing many patients who have internal neurofibromas. However, a low score, with high sensitivity, might select too many patients as high risk, which would be of no practical benefit. Therefore, different thresholds should be defined according to the clinical purpose.

Subcutaneous neurofibromas were independently associated with internal neurofibromas in our study, in keeping with earlier data (Tucker *et al.*, 2005). Furthermore, patients with subcutaneous neurofibromas were at higher risk for mortality in two different NF-1 populations, from France (Khosrotehrani *et al.*, 2003) and North America (Khosrotehrani *et al.*, 2005), respectively. None of the other three factors identified in our study have been reported previously to be associated with internal neurofibromas. However, the association linking absence of cutaneous neurofibromas to internal neurofibromas is in agreement with a previous study in which mortality was higher among NF-1 patients who had no cutaneous neurofibromas (Khosrotehrani *et al.*, 2003). The association between the presence of internal neurofibromas and age younger than 30 years is consistent with a report that most MPNSTs may develop from pre-existing internal neurofibromas, with the risk being highest at about 30 years of age (Evans *et al.*, 2002). Conversely the association between presence of internal neurofibromas and fewer than six café-au-lait spots has never been reported even though four individuals with multiple spinal tumors and no café-au-lait spots but with NF-1 mutation have been identified (Kaufmann *et al.*, 2001). The two features in the score, namely, absence of cutaneous neurofibromas and fewer than six café-au-lait spots, are unusual in NF-1 patients. Presence of at least two neurofibromas of any type and at least six café-au-lait spots are the diagnostic criteria for NF-1. However, all the patients in our study had a definitive diagnosis of NF-1. In patients younger than 30 years, the combination of internal neurofibromas, fewer than six café-au-lait spots, no cutaneous neurofibromas, and at least two subcutaneous neurofibromas constitutes a phenotype that is both distinct from classical NF-1 and particularly severe. Recently, examination of the phenotypic correlations between affected relatives in 750 NF-1 patients from 275 multiplex families collected through the NF-France Network provided evidence that genetic modifiers, unlinked to the NF-1

locus, contribute to the variable expressivity of the disease (Sabbagh *et al.*, 2009). However, biological factors that influence the NF-1 risk of morbidity–mortality are not known.

In sum, we developed a simple scoring system (the NF-1Score) that accurately predicted the presence of internal neurofibromas in patients with NF-1. The NF-1Score could be used to identify NF-1 patients who require particularly close monitoring for internal neurofibromas.

MATERIALS AND METHODS

Population and study samples

Patients meeting the diagnostic criteria for NF-1 established at the National Institutes of Health Consensus Development Conference (Conference statement, 1988) were included prospectively by the French NF network (Réseau NF-France). We used two samples for our study. The development sample, used to develop the prediction score, comprised 208 adults (17 years or older) included in an ongoing prospective multicenter case–control study (begun in 2005) designed to assess whether subcutaneous neurofibromas were associated with several types of internal neurofibromas. All patients in this sample were carefully investigated by MRI to determine with confidence whether internal neurofibromas were present. The validation sample was composed of the 191 NF-1 patients who were prospectively included in the Réseau NF-France database from June 2003 to June 2008, and who met the following criteria: 17 years or older, probands or sporadic disease, known internal neurofibroma status, and non-inclusion in the above-mentioned case–control study (Figure 1). The study was approved by the institutional review boards of Île-de-France IV (Paris, France) and informed consent was obtained from all patients. The study adhered to the Declaration of Helsinki Principles.

Data collection

Demographic information (age and sex) and clinical features recorded in the databases were collected during routine clinical assessments at neurofibromatosis clinics (Table 1). Detailed information was available on the dermatological characteristics: number of café-au-lait spots (0, 1, 2, 3, 4, 5, 6, $\geqslant$7), number of cutaneous neurofibromas (0, 1, 2–9, 10–99, $\geqslant$100), number of subcutaneous neurofibromas (0, 1, 2–9, 10–99, $\geqslant$100), and number and location of plexiform neurofibromas. Among clinical features, we selected those known to be associated with mortality: absence of cutaneous neurofibromas, facial asymmetry, at least two subcutaneous neurofibromas, and male gender (Khosrotehrani *et al.*, 2003, 2005). We recorded the following features as present or absent: orthopedic complications (scoliosis and pseudarthrosis), neurological abnormalities (headache, epilepsy and learning disabilities), hypertension, and renal artery stenosis.

Classification of patients: identification of internal neurofibromas

All patients in the development sample underwent standardized MRI of the spinal cord and nerve roots using non-contrast-enhanced T1- and T2-weighted sequences (coronal plane) and short-tau inversion-recovery (STIR) sequences. Paraspinal neurofibromas were characterized as diffuse or focal and as <3 or $\geqslant 3$ cm. Patients were classified as having internal neurofibromas if they had at least one diffuse paraspinal neurofibroma or at least one focal paraspinal neurofibroma measuring at least 3 cm. Patients with neither criterion were classified as not having internal neurofibromas (Drouet *et al.*, 2004; Mautner *et al.*, 2006).

In the validation sample, MRI was not performed routinely (Pinson *et al.*, 2001). MRI or computed tomography is usually recommended when there is evidence of internal neurofibromas on other imaging studies (chest radiograph or abdominal sonogram) or when symptoms such as pain or neurological deficits suggest internal neurofibromas. Patients in the validation sample were classified as having internal neurofibromas when the variable ''paraspinal neurofibromas'' was coded ''yes'' in the database and as not having internal neurofibromas when this variable was coded ''no''. No information was available on the size or location of internal neurofibromas in the validation sample.

Statistical analysis

Data were analyzed using STATA software version 8 (Stata, College Station, TX). All tests were two-tailed and *P*-values no greater than

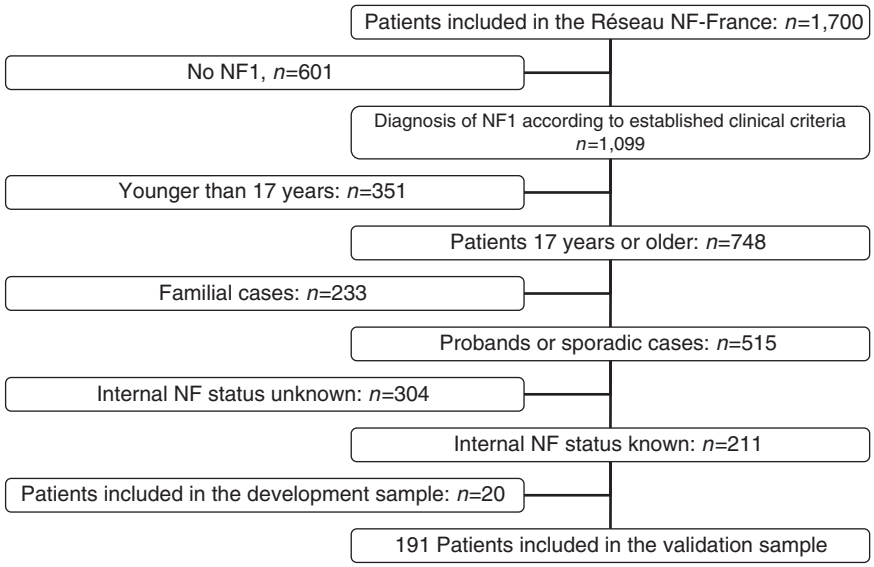

Figure 1. Flow chart of the validation sample.

0.10 were considered for prognostic modeling (Steyerberg *et al.*, 2000). The characteristics of the development and validation samples were described. The characteristics of the patients who were not included in the validation sample because their internal neurofibroma status was unknown, were compared to those of the patients included in the validation sample. Quantitative variables are either reported as median ± SD or converted to categorical variables. Thus, age was dichotomized according to the peak MPNST incidence in NF-1 patients (<30 or $\geqslant 30$ years) (Evans *et al.*, 2002). Qualitative variables are reported as number (%).

Model development

The characteristics of patients with and without internal NF were compared in univariate analyses using the χ^2-test or Fisher's exact test, as appropriate. Odds ratios (ORs) were estimated with their 95% CIs, using logistic regression models. Two-by-two analyses were also performed to assess potential interactions and confounding by fitting multiplicative models. Variables yielding *P*-values less than 0.15 in the univariate analyses were entered into a multiple logistic regression model. The final model included the variables independently associated with the presence of internal neurofibromas. Performance of the model, including calibration and discrimination, was evaluated by computing the Hosmer–Lemeshow statistic (Hosmer and Lemeshow, 1989) and the AUC-ROC (Hanley and McNeil, 1982), respectively. The Hosmer–Lemeshow test evaluates whether the predicted probabilities agree with the observed probabilities. Discrimination is the ability to distinguish patients with internal neurofibromas from those without internal neurofibromas.

Then, we used the variables identified by the multivariate analysis to build a simple-to-use score for predicting the presence of internal neurofibromas. Points were assigned to each variable on the basis of the regression coefficients in the final model: the β-coefficient was multiplied by 10 and the result was rounded to the nearest integer (Le Gall *et al.*, 1993). We checked whether the predictive performance of these rounded coefficients was similar to that of the original coefficients. The score was calculated for each patient and a multiple logistic regression equation was used to convert the score into a probability of having internal neurofibromas: the logit ($\alpha + \beta$Score) was computed and the probability was then estimated as $P = e^{\text{logit}}/(1 + e^{\text{logit}})$.

Model assessments

Internal validation. As the development sample comprised only 208 patients, we used bootstrapping to estimate shrinkage coefficients (van Houwelingen and Le Cessie, 1990) to avoid over-optimism (Miller and Hui, 1991; Steyerberg *et al.*, 2004) and to obtain nearly unbiased estimates of the predictive accuracy of the model (Harrell *et al.*, 1996). We drew 1,000 samples at random. The logistic regression coefficients were re-estimated in the bootstrap samples.

External validation. Performance of the model, including calibration and discrimination, was assessed in the validation sample.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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